CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205879Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 205879
Review #1
Review Date (see page 6)

Drug Name/Dosage Form	canagliflozin and metformin hydrochloride extended release tablet
Strength	50/500, 150/500, 50/1000, 150/1000 mg/mg canagliflozin/metformin hydrochloride
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Janssen Pharmaceuticals

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	11/20/2015
0003	2/9/2016
0007	5/19/2016
0009	6/10/2016
0010	7/15/2016
0000	11/20/2015

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products II/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
API	Martin Haber	DNDAPI/ONDP
Drug Product	Elise Luong	New Drug Products II/ONDP
Biopharmaceutics	Hansong Chen	Biopharmaceutics/ONDP
Process	Shujun Chen	Process Assessment II/OPF
Microbiology	Shujun Chen	Process Assessment II/OPF
Facility	Brian Ryan	Inspectional Assessment/OPF
Environmental Assessment	James Laurenson	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	II	(b)(4)	(b) (4)	Adequate	4/7/2016	
	IV			by E. Luong/D. Christodoulou Adequate information provided in the NDA, no review of the DMF is needed.		
	III			by E. Luong/D. Christodoulou Per MAPP "CMC Reviews of Type III DMFs for (b)(4) the referenced Type III DMFs need not be reviewed for solid dosage forms.		
	III					
	III					
	III					
	III					
	III					

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21748	Glumetza(metformin HCl) Authorized reference from applicant (Salix)
NDA	204042	Invokana (canagliflozin) Same applicant
NDA	204353	Invokamet (canagliflozin/metformin HCl) Same applicant

2. CONSULTS: not applicable

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (including the Overall Manufacturing Inspection Recommendation) is for **APPROVAL**.

Labeling comments will be finalized during the multi-disciplinary review managed by OND.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

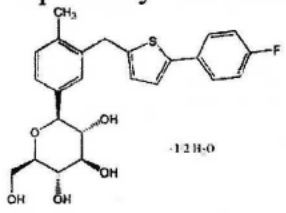
II. Summary of Quality Assessment

This is a 505(b)(1) application but not for an New Molecular Entity. The applicant has two approved NDAs for canagliflozin: NDA 204042 (canagliflozin) and NDA 204353 (canagliflozin/metformin HCl IR). NDA 204042 was approved as an NME NDA. This new NDA is for canagliflozin/metformin HCl extended release, with the canagliflozin component (formulation and manufacturing process) being based on the development of the approved NDAs. In addition, the applicant has full right of reference to the approved NDA 21748 for the metformin HCl extended release component.

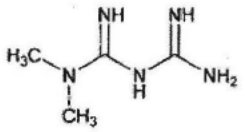
A. Drug Substance

Chemical Name or IUPAC Name/Structure:

Canagliflozin is an inhibitor of sodium glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin is chemically known as (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are C24H25FO5S•1/2 H2O and 453.53, respectively. The structural formula for canagliflozin is:



Metformin hydrochloride is N,N-dimethylimidodicarbonimidic diamide hydrochloride, with a molecular formula of C4H11N5•HCl and a molecular weight of 165.63. The structural formula is:



· HCl

NDA 204042 Invokana (canagliflozin) tablets, by the same applicant, is referenced for all CMC information on the drug substance canagliflozin. The NDA is currently approved and the reference is adequate.

DMF [redacted](b)(4) is referenced for all CMC information on the drug substance metformin HCl. The DMF is currently adequate.

B. Drug Product

The product is a bilayer film-coated tablet consisting of immediate release canagliflozin and extended release metformin HCl, with four strengths: 50/500, 150/500, 50/1000, 150/1000 mg/mg canagliflozin/metformin hydrochloride.

The canagliflozin layer is based on the approved Invokana tablets of NDA 204042: the same formulation isused in the 150/500 and 150/1000 strengths, and same formulation with the addition of silicified microcrystalline cellulose [redacted](b)(4) is used in the 50/500 and 50/1000 strengths.
The metformin layer is based on the approved Glumetza tablets of NDA 21748 (applicant of NDA 21748 provides a letter of authorization for this reference): the same formulation (with [redacted](b)(4) polyethylene oxide and hypromellose [redacted](b)(4)) is used in the 50/500 and 150/500 strengths, and a modified formulation with [redacted](b)(4) polyethylene oxide as [redacted](b)(4) excipient is used for the 50/1000 and 150/1000 strengths. The controlled release is achieved via passive diffusion through the polymer matrix with tablet erosion.

- 50/500 mg/mg canagliflozin/metformin hydrochloride tablets are oblong, biconvex, almost white to light orange film coated tablets with "CM1" on one side. A thin line on the tablet side may be visible.
- 150/500 mg/mg canagliflozin/metformin hydrochloride tablets are oblong, biconvex, [redacted](b)(4) film coated tablets with [redacted](b)(4) on one side. A thin line on the tablet side may be visible.
- 50/1000 mg/mg canagliflozin/metformin hydrochloride tablets are oblong, biconvex, [redacted](b)(4) film coated tablets with [redacted](b)(4) on one side. A thin line on the tablet side may be visible.
- 150/1000 mg/mg canagliflozin/metformin hydrochloride tablets are oblong, biconvex, reddish brown, film coated tablets with "CM4" on one side. A thin line on the tablet side may be visible.

Excipients are croscarmellose sodium, hydroxypropyl cellulose, hypromellose, lactose anhydrous, magnesium stearate (vegetable-sourced), microcrystalline

cellulose, polyethylene oxide, and silicified microcrystalline cellulose (50 mg/500 mg and 50 mg/1,000 mg tablets only). The tablets are finished with a commercially available film-coating consisting of the following inactive ingredients: macrogol/PEG3350, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide red, iron oxide yellow, and iron oxide black (50 mg/1,000 mg and 150 mg/1,000 mg tablets only).
Lactose anhydrous is [redacted] (b)(4)

The product manufacturing process consists of the manufacture of the canagliflozin granulate by [redacted] (b)(4) and the metformin HCl granulate [redacted] (b)(4)

The commercial manufacturing process was used to produce the bioequivalence (BE) and stability batches with 500 mg and 1000 mg metformin HCl granulates at Janssen Ortho and batches with 500 mg metformin HCl granulate [redacted] (b)(4). The manufacturing process of the 1000 mg metformin HCl granulate at [redacted] (b)(4) was optimized after the production of BE batches, with adequate comparability demonstration by dissolution data and stability data (one drug product batch of each strength made with the commercial [redacted] (b)(4) 1000 mg metformin HCl granulate).

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. Limits on degradants are the same as for the approved canagliflozin/metformin HCl product, including the [redacted] (b)(4) which is the same as for the 2 approved products (NDA 204042 S-9 and NDA 204353 S-5).

Container Closure: HDPE bottles with desiccant and [redacted] (b)(4).

Expiration Date & Storage Conditions: 24 months at room temperature.
Stability data include 4 batches of each strength (16 batches total) packaged in all the commercial container closure systems, manufactured at the commercial sites (3 batches of each strength with the metformin granulate from Janssen Ortho and one batch of each strength with the metformin granulate from [redacted] (b)(4), and scale. The NDA includes data from 18 months at 25 °C/60% RH and 30 °C/75% RH and, for 6 months at 40 °C/75% RH. Adequate stability data are provided to support the revised drug substance manufacturing process approved in NDA 204042 S-9 and NDA 204353 S-5, with data from one batch of each strength using canagliflozin from the revised process.

Environmental Assessment: The applicant provided an environmental assessment (EA) for canagliflozin and metforim, relying primarily on the Tier 1 testing described in the EA Guidance. The EA contains sufficient information for the determination that the proposed action does not appear to significantly affect the environment. A finding of no significant impact (FONSI) is recommended.

C. Summary of Drug Product Intended Use

Proprietary Name	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	canagliflozin and metformin hydrochloride extended release tablet
Non Proprietary Name of the Drug Substance	canagliflozin and metformin hydrochloride
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	not applicable

D. Biopharmaceutics Considerations

All four dosage strengths, with the commercial formulations, were used in pivotal BE studies (no biowaiver request). Each study used one product batch per strength manufactured with the metformin HCl granulate from each drug product manufacturer (Janssen Ortho (b)(4)

The in vitro alcohol dose-dumping study found no dose-dumping issue.

Adequate data have been provided in support of the final dissolution test method and acceptance criteria.

Adequate Physiology Based Pharmacokinetics modeling and simulation data show that different particle sizes of canagliflozin within the acceptance criteria have no impact on bioavailability and that the drug product dissolution method is over-discriminating (for example, canagliflozin with a slower dissolution profile would be bioequivalent to canagliflozin with a faster dissolution profile).

E. Novel Approaches: not applicable

F. Any Special Product Quality Labeling Recommendations: not applicable

G. Life Cycle Knowledge Information (see Attachment)

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature: I concur with the reviewers' conclusions.

Suong T. Tran -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.08.17 12:01:54 -04'00'

Su (Suong) Tran, PhD

ASSESSMENT OF THE BIOPHARMACUETICS

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Applicant's Response:

Reviewer's Assessment:

BIOPHARMACEUTICS ASSESSMENT

1. Drug Product:

The Applicant's proposed product is a fixed dose combination (FDC) drug that is a bilayer tablet containing immediate release canagliflozin and extended release metformin. Four strengths of the FDC tablets are being proposed by the Applicant, which are listed in the following table:

Table 1. Internal Formula Designations for the Drug Product

Formula Designation (CJNJ-1158196-AAC-GXXX)	Canagliflozin (Anhydrous) IR (mg)	Metformin HCl XR (mg)
G043	50	500
G045	50	1000
G042	150	500
G039	150	1000

The components and compositions of the products are listed in Table 2.

Table 2. Formulation Composition Statement of the Cana/Met XR FDC Tablets

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OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

Summary:

1. The dissolution method is reviewed and found acceptable.

2. The dissolution acceptance criteria for Cana/Met are as follows:

API	dissolution acceptance criteria
Canagliflozin	NLT (b)(4) % at 45 minutes
Metformin HCl	2 Hours: (b)(4) % 4 Hours: (b)(4) % 10 Hours: Not less than (b)(4) %

As the applicant committed to accept and revise, the above dissolution acceptance criteria should be implemented for release and stability testing for quality control of the proposed drug product.

3. No biowaiver is needed.

4. In Vitro Alcohol Dose-Dumping study showed no alcohol dose-dumping effect and the conclusions have been conveyed to OCP.

5. The PBPK simulation and modeling demonstrate that changes in the API particle size within the specifications limits do not influence the bioavailability of canagliflozin in the XR FDC formulations for all dose strengths.

From the Biopharmaceutics perspective, NDA 205879 Canagliflozin/Metformin XR

FDC Tablets 50 mg/500mg and 50 mg/1000mg, 150 mg/500mg, and 150 mg/1000mg has been reviewed and found **adequate**. Therefore, NDA 205879 is recommended for approval.

Hansong Chen, 8/15/2016

Secondary Review Comments and Concurrence:

I concur. 08/16/16

Tien-Mien Chen, Ph.D.

Branch II/Division of Biopharmaceutics

ONDP/OPQ

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Primary Quality Review

ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

The drug product is a [redacted] (b)(4) tablet for oral administration. Microbiological purity acceptance criteria are governed by compendia. Microbiological purity is being confirmed in accordance with USP requirements during primary stability testing conducted for product registration.

In accordance with ICH Q6A, the microbiological purity is further assured through drug substance and excipients that have been tested for microbial purity, the controlled cGMP manufacturing environment, validated equipment cleaning procedures, and validated manufacturing processes.

A detailed assessment of the drug product manufacturing process and controls was performed, including historical microbiological data for the drug substance, excipients,

[redacted] (b)(4)

(b)(4)

[redacted]

(b)(4)

[redacted]

2.3.P.7 Container/Closure System

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment: N/A

As this is a low microbial risk simple solid oral drug, this information is not applicable.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment:

Refer to the Drug Product review.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

Refer to the Drug Product review.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate

Shujun Chen, Ph.D., 08/04/2016

Secondary Review Comments and Concurrence: Concur.

Pei-I Chu, Ph.D., 08/09/2016

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ASSESSMENT OF ENVIRONMENTAL ANALYSIS

1. Is the applicant's claim for categorical exclusion acceptable?
   Yes. It is acceptable.

2. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Janssen Pharmaceuticals (JRD) evaluated the environmental impacts of canagliflozin and metformin drug substances according to 21 CFR Part 25. The calculated Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-aquatic based on use) was more than 1 part per billion, based on the fifth year projection forecast). JRD provided a report for fate and acute effects testing results in the NDA.

Reviewer's Assessment:
Environment Assessment (EA) for NDA 205879 has been evaluated by the EA review team, and has concluded that the sponsor's report is adequate. (Refer to the separate EA IQA section.)

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: ADEQUATE.

Elise T. Luong -S (Affiliate)

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Date: 2016.07.22 10:42:35 -04'00'

Secondary Review Comments and Concurrence:

I concur with the reviewer's assessment.

Danae D. Christodoulou -S

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

INVOKAMET XR [redacted](b)(4) is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.

Limitations of Use

[redacted](b)(4) 1 diabetes or [redacted](b) (4) diabetic ketoacidosis.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	INVOKAMET Canagliflozin/metformin	Adequate
Dosage form, route of administration	Extended Release Tablets/Oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	50mg/500mg 150mg/500mg 50mg/1000mg 150mg/1000mg	Adequate

Conclusion: The information provided is adequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

The 50mg/500mg tablets are almost white to light orange with "CM1" on one side, the 50mg/1000mg tablets are pink with "CM3" on one side, the 150mg/500mg tablets are orange with "CM2" on one side, and the 150mg/1000mg tables are reddish brown with "CM4" on one side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Canagliflozin/Metformin Tablet	Adequate
Strengths: in metric system	50mg/500mg 150mg/500mg 50mg/1000mg 150mg/1000mg	The 4 strength levels are described in the application as well and acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	3.2.P.1-1	Adequate

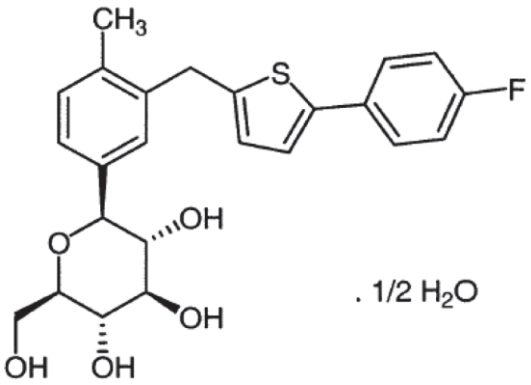
Conclusion:
The full description of different tablet strengths of the CANA/MET XR FDC is described in the NDA. The information is acceptable.

#11: Description (21CFR 201.57(c)(12))

INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes: canagliflozin and metformin hydrochloride.

Canagliflozin:

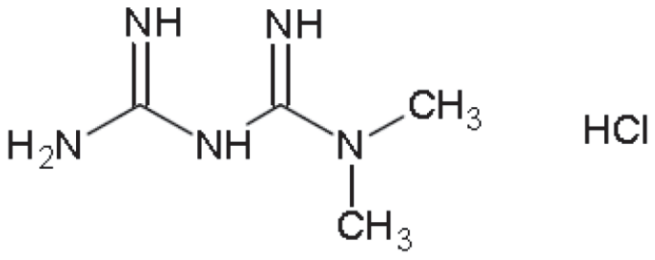
Canagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin is chemically known as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are $C_{24}H_{25}FO_5S \cdot 1/2\ H_2O$ and 453.53, respectively. The structural formula for canagliflozin is:



Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9.

Meformin Hydrochloride:

Metformin hydrochloride is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is chemically known as 1,1-Dimethylbiguanide hydrochloride and its molecular formula and weight are $C_4H_{11}N_5 \cdot HCl$ and 165.62, respectively. The structural formula for metformin hydrochloride is:



Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

INVOKAMET XR

INVOKAMET XR is supplied as film-coated tablets for oral administration. Each 50 mg/500 mg tablet and 50 mg/1,000 mg tablet contains 51 mg of canagliflozin equivalent to 50 mg canagliflozin (anhydrous) and 500 mg or 1,000 mg metformin hydrochloride. Each 150 mg/500 mg tablet and 150 mg/1,000 mg tablet contains 153 mg of canagliflozin equivalent to 150 mg canagliflozin (anhydrous) and 500 mg or 1,000 mg metformin hydrochloride.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	INVOKAMET Canagliflozin/metformin	Adequate
Dosage form and route of administration	Extended Release Tablets/Oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	This information is provided in section 3.2.P.1 *Description and Composition of the Drug Product*	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Canagliflozin is antihyperglycemic agent (AHA) inhibition of renal SGLT2, blocking renal glucose reabsorption. Metformin belongs to the biguanide class of antihyperglycemic agent that improve glucose tolerance in patients with type 2 diabetes.	Adequate
Chemical name, structural formula, molecular weight	Information is provided above	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9. Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4.	Adequate

Conclusion:
The required information has been provided in the application, and is adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets are available in the strengths and packages listed below:

Canagliflozin 50 mg and metformin hydrochloride 500 mg extended-release tablets are oblong, biconvex, almost white to light orange, film-coated tablets with "CM1" on one side. A thin line on the tablet side may be visible.

- NDC 50458-940-01 Bottle of 60

Canagliflozin 50 mg and metformin hydrochloride 1,000 mg extended-release tablets are oblong, biconvex, pink, film-coated tablets with "CM3" on one side. A thin line on the tablet side may be visible.

- NDC 50458-941-01 Bottle of 60

Canagliflozin 150 mg and metformin hydrochloride 500 mg extended-release tablets are oblong, biconvex, orange, film-coated tablets with "CM2" on one side. A thin line on the tablet side may be visible.

- NDC 50458-942-01 Bottle of 60

Canagliflozin 150 mg and metformin hydrochloride 1,000 mg extended-release tablets are oblong, biconvex, reddish brown, film-coated tablets with "CM4" on one side. A thin line on the tablet side may be visible.

- NDC 50458-943-01 Bottle of 60

Storage and Handling
Store at 68° to 77°F (20° to 25°C); excursions permitted between 59°F and 86°F (15°C and 30°C) [see USP Controlled Room Temperature]. Store in the original container.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Canagliflozin/metformin 50mg/500mg 150mg/500mg 50mg/1000mg 150mg/1000mg	The strengths of the tablets have been described in the application and are acceptable
Available units (e.g., bottles of 100 tablets)	Bottles of 60	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	50mg/500mg tablet is white to light orange, oblong, bixonvex, film-coated with "CM1" on one side. 150mg/500mg tablet is orange, oblong, biconvex, film-coated with "CMC2" on one side. 50mg/1000mg tablet is pink, oblong, biconvex, film-coated with "CM3" on one side. 150mg/1000mg tablet is reddish brown, oblong, biconvex, film-coated with "CM4"on one side.	Adequate. The description of all strengths have been provided in the NDA.
Special handling (e.g., protect from light, do not freeze)	Store in the original container.	Adequate
Storage conditions	Store at 68° to 77°F (20° to 25°C); excursion permitted between 59° to 86°F (15° to 30°C) [See USP Controlled Room Temperature].	The storage condition is supported by data and is acceptable.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: Janssen Ortho, LLC Gurabo, PR 00778 Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560	Adequate

Conclusion:
The information has been provided in the application and is adequate.

2. Container and Carton Labeling

1) Immediate Container Label

(b)(4)

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(b)(4)

Reviewer's Assessment: Adequate.

The immediate label has all the relevant information in accordance with regulatory requirements. The labels are acceptable from the DP reviewer's perspective.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name INVOKAMET and the established name Canagliflozin and Metformin satisfy the font size deferential required by 21CFR 210.10(g)(2)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Four strengths are described in the application for approval	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	The net contents I terms of weight and counts are indicated as per regulation	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	N/A	
Lot number per 21 CFR 201.18	Provision for lot number is indicated in the label	Adequate
Expiration date per 21 CFR 201.17	Location for expiration date is provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement "Rx only" is indicated on the label	Adequate
Storage	The storage condition is indicated	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR	NDC number is provided	Adequate

Bar Code per 21 CFR 201.25(c)(2)***	The position for a bar code is provided on the label	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured by: Janssen Ortho, LLC Gurabo, PR 00778 Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560	Adequate
Others	**Keep out of reach of children**	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

***Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:
The information provided on the label met the regulatory requirements and is acceptable.

2) Carton Labeling

Carton labeling is not a requirement. There is no carton labeling in the NDA.

Conclusion:
The labels as presented are adequate from the DP reviewer's perspective. Labeling will be finalized at a later date as part of the review team's labeling negotiation.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Elise T. Luong -S (Affiliate)

Digitally signed by Elise T. Luong -S (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0010300159, cn=Elise T. Luong -S (Affiliate)
Date: 2016.07.22 10:43:31 -04'00'

Secondary Review Comments and Concurrence:

I concur with the reviewer's assessment.

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.07.22 11:20:17 -04'00'

ENVIRONMENTAL ANALYSIS

[Suggested exec. summary: The applicant provided an environmental assessment (EA) for canagliflozin and metforim, relying primarily on the Tier 1 testing described in the EA Guidance. FDA concludes that (1) the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) the proposed action does not appear to significantly affect the environment. A finding of no significant impact (FONSI) is recommended. Additional FDA monitoring of potential impacts from metformin is warranted outside of this subject action due to the potential for cumulative impacts beyond the use addressed by this application, to the increasing use of metformin over time, and to the potential for endocrine effects.]

R Regional Information

Environmental Analysis

This use is expected to result in increases in the release of each of the two APIs, canagliflozin and metforim, into the environment. The applicant submitted an EA that is similar to a previous EA by the applicant for these same APIs, NDA 204353. The previous EA was reviewed by FDA October 18, 2013 and found to be adequate for approval because it contained sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment. Furthermore, the results of the risk characterizations in the EA, and the review conducted by FDA, suggested that the specific use of the NDA 204353 tablets would not significantly impact the environment. Based on the information available to date at the time, a finding of no significant impact (FONSI) was recommended for the previous NDA.

For both the current and previous NDAs, the applicant provided partition coefficient (log K_{ow}) and adsorption coefficient (K_{oc}) data, noting that chemicals with these levels do not have the potential to bioaccumulate or adsorb to biosolids, but rather will move primarily into the aquatic environment. The applicant also has used screening-level assumptions, such as no depletion, to develop maximum expected environmental concentrations (MEECs)—referred to as the expected introductory concentration (EIC) in the review portions of this memorandum—which were compared to the lowest acute no-observed effects concentrations (NOECs) for canagliflozin and metformin, resulting in assessment factors (AFs) greater than (b) (4) for both EAs. In addition, no sublethal effects were observed at the EICs. The microbial inhibition tests, which are primarily for assessing the potential for the compound to disrupt waste treatment processes, indicated that both canagliflozin and metformin from this application, as well as cumulatively for all uses of these substances, would have virtually no potential to disrupt waste treatment processes. As described in the EA Guidance, this information indicates that the application for canagliflozin/metformin would have no significant impact on the environment.

FDA conducted additional confirmatory analysis during the review of the previous EA to assess the potential for these drugs to be highly active toxicologically (i.e., with aquatic toxicity affects below 1 ppb, or µg/L). Specifically, a chronic toxicity value of (b) (4) µg/L for canagliflozin was developed based on the lowest acute NOEC of (b) (4) mg/L and a screening-level adjustment factor of (b) (4) for non-hormonally active drugs. The EIC of (b) (4) µg/L for canagliflozin was less than this chronic toxicity value with a margin of

exposure (MoE) of (b) (4) Similarly, a chronic toxicity value of 44 µg/L was found for metformin in the literature. The EIC of (b) (4) µg/L for metformin was less than this toxicity value with an MoE of (b) (4). These comparisons indicated a low likelihood of adverse aquatic effects due to this application, especially once dilution and depletion mechanisms are taken into account. Furthermore, the applicant stated, the modes of action (MOAs) for these two products did not appear to be related to MOAs associated with highly active pharmaceuticals, such as hormonally active MOAs identified in recent FDA guidance (USFDA, 2016).

Cumulative impacts from all uses of these drugs in the US were also assessed previously by FDA. These impacts appeared to be low. The canagliflozin EIC represented all uses of this drug in the US, and the MOA appeared to be somewhat unique. Thus the above assessment was considered complete with regard to cumulative (total additive) exposure to this substance. The metformin use from this application, however, was only about (b) (4)% of the total use of metformin. A worst-case EIC based on total use of metformin would have been approximately (b) (4) µg/L. This EIC was higher than measured concentrations in surface waters. Applying conservative estimates of dilution to that EIC, as well as reductions due to human metabolism and wastewater treatment, resulted in an expected environmental concentration (EEC) of approximately (b) (4) µg/L. This concentration results in an MoE of approximately (b) (4) compared to the chronic toxicity value of (b) (4) µg/L. Thus, there did not appear to be a significant impact from cumulative (total additive) exposure to metformin in the aquatic environment.

For this current EA, the estimated EICs are (b) (4) µg/L for canagliflozin and (b) (4) µg/L for metformin based on the highest five-year use projection and assuming no metabolism and the worst-case scenario of all drug API entering the aquatic environment, as recommended in the EA Guidance. These EICs therefore exceed the categorical exclusion EIC of 1 µg/L noted in 21 CFR 25.31(b), and thus pursuant to 21 CFR 25.15(a), the applicant provided an EA. The previous EA's EICs were (b) (4) µg/L and (b) (4) µg/L for canagliflozin and metformin, respectively. The current EICs are (b) (4)% and (b) (4)% higher than the previous EICs, respectively.

The main goals of this review are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

Reviewer's Assessment:
Given the similarities of the current and previous EAs and the FDA review of the previous EA, FDA has concluded that a full re-review of the EA is not required to determine the environmental impact. Several issues were identified related to this EA, however:

1. As noted in the applicant's Overall Reviewers Guide, in Module 1.2, Cover Letters, of the application's Common Technical Document (CTD), this product is intended to be used in the same adult population for which the previous NDA product is recommended, which could be considered to result in no increased use of the product. This in turn would negate the need for an EA (21 CFR 25.31(a)). Module 1.2 also notes, however, that this product offers an opportunity to simplify regimens by reducing pill burden, potentially resulting in improved regimen adherence. This improved adherence could result in increased use, which could be reflected in part in the higher EICs noted above. Thus, the development of an EA is appropriate given the combination of increased use and EICs greater than 1 ppb.

2. The new EICs are substantially higher than the previous EICs. Therefore, the comparison of the EICs to toxicity values will be of particular focus.

3. New environmental risk information may have been developed since the previous EA. Therefore, an updated literature search was conducted.

Prior to addressing the second item above, an updated search of environmental data per the third item was conducted. For canagliflozin, no new data were found. For metformin, an updated literature search identified several new studies of interest. Some studies found potential endocrine effects from metformin or its transformation products in aquatic organisms at near-environmentally relevant concentrations. One of these studies notes that the link between insulin signaling and steroidogenesis indicates the potential for antidiabetic drugs including metformin to act as endocrine disruptors (Niemuth et al., 2015). This study found that metformin treatment in fathead minnows for four weeks at 40 µg/L induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of an MOA related to endocrine disruption. This *de facto* lowest observed effects concentration (LOEC) of 40 µg/L is lower than the previous implicit LOEC of >44 µg/L. This implicit LOEC was derived from the ECOSAR model, which defines its chronic values as the geometric mean of the NOEC and the LOEC (USEPA, 2012). Thus, a chronic ECOSAR value of 44 µg/L would by definition be associated with a LOEC that is higher than 44 µg/L. Similarly, a LOEC of 40 µg/L would be associated with a NOEC (or other lower chronic value for purposes of comparison to an EEC) of less than 40 µg/L. In this particular case, however, the mRNA effect is only an indicator of possible endocrine effects rather than an indicator of significant adverse population-level impacts. The study by Niemuth et al. (2015) found no effect on fathead minnow fecundity. Furthermore, a 40 µg/L LOEC reflects an MoE of approximately 44 times an updated EEC of (b) (4) µg/L. This updated EEC is based on extrapolating current overall use data to 2016 from 2014 levels (IMS, 2014) and applying the same metabolism, treatment, and dilution factors used in the previous EA review. The 40 µg/L LOEC also is higher than new concentration data in surface waters that range from 0.06 µg/L to 3 µg/L (Niemuth et al., 2015).

A second study noted that a metformin transformation product, guanylurea, needs further research (Kosma et al., 2015). A third study on human drinking water screening benchmarks included a benchmark of 4 µg/L for metformin (Suchomel et al., 2015). The EEC of (b) (4) µg/L is also below this level, with an MoE of (b) (4)

Thus, based on a review of the EA and an updated literature search, FDA concludes the following:

1. The log K_{ow} values, < (b) (4), indicate a low bioaccumulation potential, and the Koc values, << (b) (4), indicate that these compounds will not tend to adsorb to biosolids. Thus, assumptions regarding the movement of these drugs primarily into the aquatic environment are reasonable.

2. It is reasonable to continuing assuming no environmental depletion mechanisms or metabolites for either canangliflozin or metformin.

3. The applicant's use of a screening-level scenario, in which 100% of the product will remain in the aquatic environment following wastewater treatment and discharge of effluents, is reasonable.

4. Canagliflozin would have virtually no potential to disrupt waste treatment processes, and metformin presents a low risk.

5. Canagliflozin data support the default conclusion in the EA Guidance that an AF of greater than (b) (4) provides sufficient confidence of no adverse effects at the EIC. For example, the EIC of (b) (4) µg/L is less than the chronic toxicity value of (b) (4) µg/L.

6. An updated EEC of (b) (4) µg/L for metformin, based on extrapolating current overall use data (IMS, 2014), has an MoE of approximately (b) (4) compared to a possible LOEC of (b) (4) µg/L.

7. There appears to be some potential for antidiabetic drugs to act as endocrine disruptors, and thus additional FDA monitoring of potential cumulative and other impacts from this class of drugs and MOAs is warranted outside of this subject action, such as through future environmental assessments and/or the requesting of additional data from sponsors.

Conclusions

The EA is adequate for approval of the NDA. The EA contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and additional reports and on the scientific validity of the "no significant effects" conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA. Therefore, based on the information available to date, a FONSI is recommended for this application.

References

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USEPA. 2012. Methodology Document for the ECOlogical Structure-Activity Relationship Model (ECOSAR) Class Program. US Environmental Protection Agency, Washington, DC.

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. Center for Biologics Evaluation and Research. US Food and Drug Administration, Rockville, MD.

QUALITY ASSESSMENT

USFDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Biologics Evaluation and Research. US Food and Drug Administration, Rockville, MD.

Primary EA Reviewer Name and Date: James Laurenson, EA Reviewer, OPQ/ONDP, July 8, 2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Attachment

Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Drug content/Assay	Formulation Process Container closure	H	stability studies in-process controls	L	none
Impurities/ degradants	Formulation Process Container closure	H	stability studies in-process controls	L	none
Appearance	Formulation Process Container closure	H	stability studies in-process controls	L	none
Dissolution/drug release rate (including alcohol dose dumping)	Formulation Particle size (b)(4)	H	see Biopharmaceutics review	L	none
Hardness/friability	Formulation Process	H	in-process controls	L	none
Content uniformity	Process	H	in-process controls	L	none